Extracellular vesicles study outlines new strategies to combat neurodegenerative diseases

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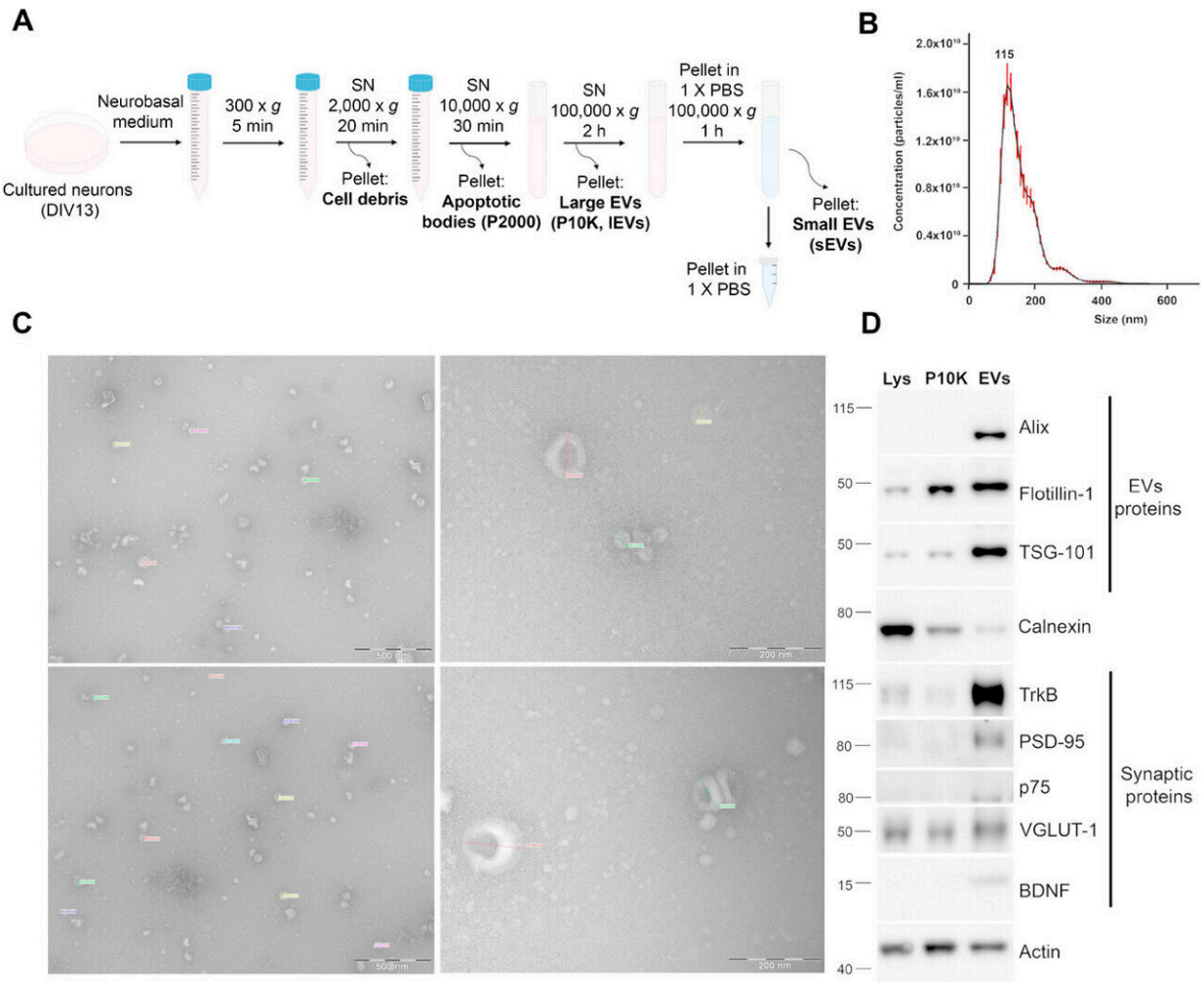

EVs derived from cortical neurons are enriched in synaptic proteins. EVs were isolated from cortical neurons culture media at DIV13 following a sequential UC protocol. (A) Schematic representation of the EVs isolation procedure. Cell

debris, apoptotic bodies (P2000) and large EVs (P10K) were discarded during the isolation process, and small EVs (sEVs) were obtained. SN, supernatant. (B) Size distribution of particles by NTA. Red lines indicate the standard deviation. 115 nm represents the most frequent particle size. (C) TEM micrographs show particles with the characteristic morphology and size of small EVs. (D) Samples were subjected to WB and EVs markers (Alix, Flotillin-1, TSG-101) and synaptic proteins (TrkB, PSD-95, p75NTR, VGLUT-1 and BDNF) were analyzed. Calnexin was used as an EVs negative control. Lys, neuronal lysate. Full length WB can be found in Figure S12. Credit: *Journal of Extracellular Vesicles* (2023). DOI: 10.1002/jev2.12355

A new study by the University of Barcelona could drive the design of future strategies to regenerate damaged brain areas in neurodegenerative diseases. The study emphasizes the role of neuron-derived extracellular vesicles in the processes that modulate synaptic plasticity and neuronal signaling pathways. In addition, the results outline a new scenario for using these extracellular vesicles derived from healthy neurons—capable of transporting molecules between cells—in treatments against neurodegenerative diseases.

The study, published in the *Journal of Extracellular Vesicles*, whose first author is the predoctoral student Julia Solana-Balaguer, was led by Professor Cristina Malagelada, from the Faculty of Medicine and Health Sciences and the Institute of Neurosciences (UBneuro) of the University of Barcelona.

Other leading researchers from UBneuro, the Faculty of Physics and the Institute of Complex Systems (UBICS) of the UB, the August Pi i Sunyer Biomedical Research Institute (IDIBAPS) and the areas of the Center for Biomedical Research Network on Neurodegenerative Diseases (CIBERNED) and Epidemiology and Public Health (CIBERESP), among others, have also taken part in the study.

Neuron-to-neuron communication

Neurons are capable of forming vesicles that transport molecules—proteins, lipids, RNA, etc.—to the outside, and regulate communication between nerve cells. These are extracellular vesicles, and even today there are still many unknowns about the role they play in communication between neurons in the nervous system.

The new study, performed with in vitro neuronal cultures from animal models, reveals that these vesicles are capable of transporting proteins—for example, PSD-95 and VGLUT-1—and other determinants of communication processes between neurons.

"Although extracellular vesicles have been proposed as regulators of intercellular communication in the brain, most studies demonstrate this in models that are far from a physiological state and in vesicles whose origin is unknown. In this study we demonstrate that, in a physiological model without pathologies, neuron-specific extracellular vesicles regulate neuron-to-neuron communication and promote synaptic plasticity," says Cristina Malagelada, professor at the UB Department of Biomedicine and researcher at the CIBERNED.

New strategies to combat neurodegeneration

Within the framework of the study, the team has applied complementary techniques to isolate the extracellular vesicles released by neurons, such as sequential ultracentrifugation or size exclusion chromatography. In addition, techniques have been used to characterize them, such as nanoparticle tracking analysis and transmission electron microscopy. These vesicles have also been used to perform treatments on healthy neurons and neurons deprived of nutrients.

"Once neuron-neuron communication is understood in a non-pathological state, we want to address this question in the context of neurodegeneration. Therefore, it is crucial to be able to characterize the vesicles released by neurons in neurodegenerative diseases in order to understand the progression of these pathologies. In addition, we want to explore if, in a pathological model, we can reverse a more neurodegenerative trait with the treatment of extracellular vesicles derived from healthy neurons," concludes the researcher.

More information: Julia Solana-Balaguer et al, Neuron-derived extracellular vesicles contain synaptic proteins, promote spine formation, activate TrkB-mediated signalling and preserve neuronal complexity, *Journal of Extracellular Vesicles* (2023). DOI: 10.1002/jev2.12355

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